1-Year Results of a Multicenter Randomized Controlled Trial Comparing Heparin-Bonded Endoluminal to Femoropopliteal Bypass

Reijnen, Michel M. P. J.; van Walraven, Laurens A.; Fritschy, Wilbert M.; Lensvelt, Mare M. A.; Zeebregts, Clark J.; Lemson, M. Suzanna; Wikkeling, Otmar R. M.; Smeets, Luuk; Holewijn, Suzanne

Published in:
Jacc-Cardiovascular interventions

DOI:
10.1016/j.jcin.2017.09.013

Publication date:
2017

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 22, 2017
ISSN 1936-8798
https://doi.org/10.1016/j.jcin.2017.09.013

1-Year Results of a Multicenter Randomized Controlled Trial Comparing Heparin-Bonded Endoluminal to Femoropopliteal Bypass

Michel M.P.J. Reijnen, MD, PhD,[a] Laurens A. van Walraven, MD,[b] Wilbert M. Fritschy, MD, PhD,[c] Mare M.A. Lensvelt, MD, PhD,[a] Clark J. Zeebregts, MD, PhD,[d] M. Suzanna Lemson, MD, PhD,[e] Otmar R.M. Wikkeling, MD, MBA,[f] Luuk Smeets, MD, PhD,[a] Suzanne Holewijn, PhD[a]

ABSTRACT

OBJECTIVES This study sought to compare heparin-bonded endografts with femoropopliteal bypass, including quality of life, using general health and disease-specific questionnaires as well as patency rates.

BACKGROUND Endovascular treatment continues to advance and is gaining acceptance as primary treatment for long occlusive or stenotic lesions in the superficial femoral artery. Heparin-bonded expanded polytetrafluoroethylene endografts have been related to outcomes comparable to bypass surgery, but this has not been tested in a randomized fashion.

METHODS A multicenter randomized-controlled trial was performed comparing femoropopliteal bypass with heparin-bonded expanded polytetrafluoroethylene endografts. Data were analyzed on an intention-to-treat and per-protocol manner.

RESULTS A total of 129 patients were randomized and 125 patients were treated, 63 in the endoluminal and 62 in the surgical group (42 venous, 20 prosthetic). Enrollment was terminated before reaching the predefined target number for patency. Baseline characteristics and anatomical data were similar. Patients were treated for critical limb ischemia in 38.1% and 32.2% in the endoluminal and surgical arms, respectively. Mean lesion length was 23 cm in both groups and lesions were largely TransAtlantic Inter-Society Consensus II D. Hospitalization time and 30-day morbidity were significantly lower in the endoluminal group, without differences in serious adverse events (n = 5 each; surgical: 4 venous and 1 polytetrafluoroethylene bypass). There were no significant differences in Rutherford category between groups at any time point. At 30 days the endoluminal group showed a greater improvement in quality-of-life scores. At 1 year, these differences had largely disappeared and no differences in primary (endoluminal: 64.8%; surgical: 63.6%), assisted primary (endoluminal: 78.1%; surgical: 79.8%), secondary patency (endoluminal: 85.9%; surgical: 83.3%), and target vessel revascularization (endoluminal: 72.1%; surgical: 71.0%) were observed. Limb salvage rate was 100% in both groups.

CONCLUSIONS Heparin-bonded endoluminal bypass for long segment lesions shows promising results (less morbidity, faster recovery, and improvement in quality of life with indistinguishable patency rates at 1 year) compared with surgical bypass. Long-term results have to be awaited. (J Am Coll Cardiol Intv 2017;10:2320–31) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Surgery, Rijnstate, Arnhem, the Netherlands; [b]Department of Surgery, Antonius Hospital, Sneek, the Netherlands; [c]Department of Vascular Surgery, Isala, Zwolle, the Netherlands; [d]Department of Surgery, Division of Vascular Surgery, University of Groningen, Groningen, the Netherlands; [e]Department of Surgery, Slingeland Hospital, Doetinchem, the Netherlands; and the [f]Department of Surgery, Nij Smellinghe Hospital, Drachten, the Netherlands. This is an investigator-sponsored study partly supported by W.L. Gore and Associates. Drs. Reijnen, van Walraven, Fritschy, and Smeets have received speaker fees from W.L. Gore and Associates. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 29, 2017; revised manuscript received September 5, 2017, accepted September 13, 2017.

Peripheral arterial occlusive disease (PAOD) is a common condition with an increasing prevalence in an aging population. About 70% of lesions are located in the infrainguinal area and about one-half of interventions for PAOD are performed for lesions located in the femoropopliteal area (1). For decades venous femoropopliteal bypass surgery has been considered to be the gold standard to treat extensive PAOD in the superficial femoral artery. The latest version of the TransAtlantic Inter-Society Consensus (TASC) document stated that surgery should be considered as best option in lesions over 15 cm in length (2,3). However, endovascular treatment modalities in occlusive and stenotic disease continue to advance, and they are gaining broader acceptance for treatment of more complex lesions.

SEE PAGE 2332

Plain balloon angioplasty is usually reserved for short lesions only whereas bare nitinol stents have improved the outcome of endovascular treatment in intermediate-length lesions (3). More recently, alternatives have been introduced, including sirolimus and paclitaxel drug eluting-based techniques and covered self-expanding stents. All of them may improve results of endovascular therapy, especially in complex lesions. The efficacy of an expanded polytetrafluoroethylene-covered nitinol stent (Viabahn, W. L. Gore, Flagstaff, Arizona) has been shown in various case series (4–6). Randomized trials have already demonstrated their superiority in patency, without differences in clinical outcome parameters, over nitinol stents up to 2 years in more complex lesions and no differences over a 4-year period compared with prosthetic, above-the-knee, surgical bypasses (7,8). The latest generation of this endograft incorporates several adjustments with potential clinical benefit, including the integration of the heparin-bonding technology, improvement of the proximal edge design, and availability of stent grafts with a length of 25 cm, reducing the number of overlap zones. Initial cohort studies have shown 1-year primary patency rates approaching the results of the historic gold standard: the venous femoropopliteal bypass (6,9).

The current study was designed to compare the outcomes of the heparin-bonded endograft with the femoropopliteal bypass, including quality of life (QoL) and patency rates.

METHODS

The design was a multicenter prospective randomized controlled trial comparing heparin-bonded endografts to surgical bypass, on an intention-to-treat basis, with primary endpoints of 30-day QoL and 1-year primary patency. The hypothesis of the study was that treatment with the heparin-bonded endograft would provide a better QoL at 30 days with equal patency rates at 1 year compared with surgical bypass.

Patients who met the entry criteria were included in the study after providing informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the Medical Ethics committee of Nijmegen (CMO-2010-089) and the local institutional review board of each participating center. The design of the study has been previously published and was registered at ClincalTrials.gov (NCT01220245) (10).

Patients were recruited from 6 vascular centers in the Netherlands with a batched randomization with stratification per site. Due to the design the postprocedural assessment was done in a nonblinded fashion. An experience of ≥10 endoluminal bypasses was required before including patients in the trial to prevent a learning curve bias. All surgeons had at least 5 years of experience in both techniques. Patients were included with long occlusive or stenotic lesions of the superficial femoral artery with a Rutherford category 3 to 6. Patients with disabling claudication were initially treated with supervised walking exercise. Cilostazol was not routinely provided. Cardiovascular risk management was performed according to national guidelines (11).

Patients were screened by duplex ultrasound imaging and additional computed tomography angiography or magnetic resonance angiography was performed for procedural planning. Lesions were categorized according to the TASC II criteria (2,3). Angiographic and duplex ultrasound assessments were performed by local treating operators. Cardiovascular risk factors were scored according to the Society for Vascular Surgery and American Association of Vascular Surgery medical comorbidity grading systems (12). Follow-up was performed at 1, 3, 6, 12, 18, and 24 months and annually thereafter until 5 years. This included clinical evaluation; duplex ultrasound imaging; ankle-brachial index (ABI) including standardized walking test if possible; the 36-Item Short Form Survey (SF-36), as a measure of the general health status in all patients; and the Walking Impairment Questionnaire (WIQ), as a measure of disease-specific health status in patients with intermittent claudication (IC). The QoL

ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

CLI = critical limb ischemia

IC = intermittent claudication

PAOD = peripheral arterial occlusive disease

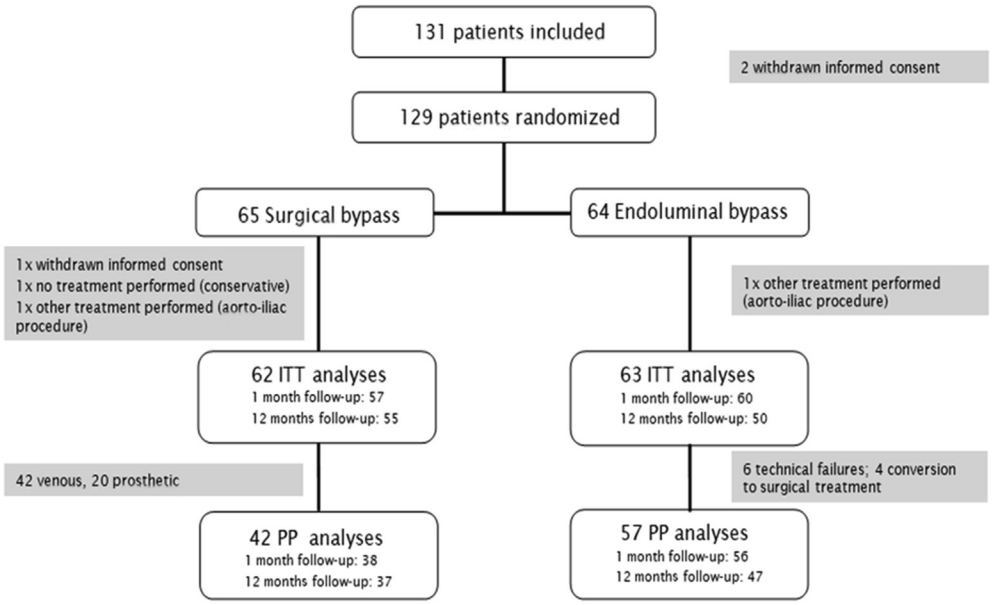
QoL = quality of life

SF-36 = 36-Item Short Form Survey

TASC = TransAtlantic Inter-Society Consensus

WIQ = Walking Impairment Questionnaire

FIGURE 1 Inclusion Flow Chart



Among the 125 treated patients, 63 were randomized in the endoluminal group and 62 were randomized in the surgical group, of which 42 were treated with a venous conduit. ITT = intention to treat; PP = per protocol.

questionnaires were completed by the patients and help from a nurse was provided when needed. The inclusion and exclusion criteria have been described previously (10).

ENDPOINTS AND DEFINITIONS. The primary endpoint of the study was QoL at 30 days as assessed by the SF-36 questionnaire and primary patency at 1-year follow-up. Secondary endpoints included primary-assisted and secondary patency, morbidity, clinical improvement, reinterventions, and target vessel revascularization. Patients with disabling IC were analyzed separately using patient-reported pain-free and maximal walking distance and the WIQ as additional endpoints. Patients with critical limb ischemia (CLI) were analyzed using major amputations as an additional endpoint.

The full list of definitions and the endovascular and surgical techniques has been published previously (10).

Post-procedurally, all patients in both groups were treated with 80 mg acetylsalicylic acid and 75 mg clopidogrel daily for the first year unless oral anticoagulation was indicated for other reasons. After 1 year single antiplatelet therapy (acetylsalicylic) was continued. All patients started statin before the intervention.

DATA COLLECTION. Data were collected by means of case report forms and entered in the central online database with audit trail ("The research manager", Deventer, the Netherlands) and controlled by monitoring. Data on adverse events during the first 30 days were reported to the data safety data monitoring board and to the accredited Central Committee on Research involving Human Subjects. An interim safety analysis was performed after inclusion of the first 40 patients.

STATISTICAL ANALYSES. Sample size calculation was performed based on the assumption that the endoluminal bypass would improve 30-day general health status, as measured by a 10-point increase in the SF-36 score. With an SD of 20, 63 patients per group were required (alpha 5%, power 80%). For a non-inferiority trial with regard to 1-year patency, with an effect size of 90% and a margin of 10%, 111 patients per group would be needed (alpha 5%, power 80%). The effect size of 90% refers to an estimated primary patency rate at 1 year in the surgical control arm.

To determine which variables followed the normal distribution, each was tested with the Kolmogorov-Smirnov test. Data were analyzed based on an intention-to-treat principle, but additional per-protocol analyses were performed for patency.

Continuous variables are presented as mean ± SD or median (range) if applicable. Differences were tested using a Student *t* test (normal distribution) or Mann Whitney *U* test (skewed distribution). Categorical variables are presented as a number followed by percentage and differences between groups were tested using chi-square analysis. Analyses of variance with repeated measures design was used to analyze changes over time in health status, Rutherford stage, and ABI. Patency rates are presented as Kaplan-Meier curves including censoring for patients lost to follow-up. Differences in survival were tested using the log-rank test.

A 2-sided p value <0.05 was considered significant. Statistical analyses were performed using SPSS version 22.0 for Windows (IBM Corporation, Armonk, New York).

RESULTS

A total of 131 patients were included in the study, 2 of whom withdrew informed consent. As a consequence, 129 patients were randomized from November 2010 to June 2015. Subsequently, another 4 patients were excluded from further analysis (Figure 1), resulting in 125 treated patients, 63 in the endoluminal group and 62 in the surgical group. Due to the low enrollment rate it was decided to terminate the study after reaching the sample size for the QoL-endpoint, since the inclusion period would become unacceptable long. Follow-up compliance at 12 months was 81.1% in the endoluminal group and 88.7% in the surgical group.

BASELINE CHARACTERISTICS. Patient demographics are depicted in Table 1; there were no significant differences between groups at baseline. In both groups the proportion of patients treated for IC and CLI were similar, as was baseline ABI and the presence of ulcerations.

The anatomical details are shown in Table 2. The vast majority of patients were treated for TASC II D lesions without differences between groups except for larger diameter of the popliteal artery and a higher proportion of flush occlusions in the surgical group.

At baseline both groups showed equal scores in all domains of the SF-36, except for a worse "mental health" domain score in the endoluminal group compared with the surgical group Table 3) and a higher score for "health change" in the endoluminal group compared with the surgical group. No differences in the separate domains of the WIQ or total WIQ score were observed between groups in patients with IC at baseline (Table 4).

TABLE 1 Baseline Characteristics of the Study Population for Both Study Groups

	Surgical (n = 62)	Endoluminal (n = 63)	p Value
Age, yrs	66.7 ± 7.9	68.5 ± 8.8	0.227
Male	80.6	73.0	0.312
Cardiovascular risk factors			
Tobacco use (current smoker)	51.6	49.2	0.788
Hypertension	74.2	68.3	0.463
Diabetes mellitus	33.9	34.9	0.902
Dyslipidemia	71.0	74.6	0.648
Cardiac disease	38.7	38.1	0.944
Pulmonary disease	27.4	17.5	0.182
Stroke	22.6	14.3	0.231
Renal insufficiency	16.1	9.5	0.269
Pre-operative medication			
Acetylsalicylic acid	79.0	90.5	0.086
Clopidogrel	8.1	12.9	0.559
Acenocoumarol	14.5	4.8	0.076
Phenprocoumon	1.6	0.0	0.315
Statin	71.7	76.2	0.682
Rutherford classification			
3	67.7	61.9	0.551
4	16.1	23.8	
5	14.5	14.3	
6	1.6	0.0	
ASA classification			
I	1.7	0.0	0.469
II	65.0	55.6	
III	31.7	42.9	
IV	1.7	1.6	

Values are mean ± SD or %.
ASA = American Society of Anesthesiologists.

TABLE 2 Characteristics of the Treated Lesions for Both Study Groups

	Surgical (n = 62)	Endoluminal (n = 63)	p Value
TASC II classification			
B	5.0	3.3	0.458
C	13.3	21.7	
D	81.7	75.0	
Lesion length, cm	23.6 ± 7.1	23.3 ± 8.3	0.857
Flush occlusion	41.0	28.3	0.182
Popliteal artery patent at P1 level	90.3	91.8	0.609
Diameter of popliteal artery, mm	5.6 ± 1.0	5.2 ± 0.8	0.012
Number of stenosis-free outflow vessels			
0	3.3	6.6	0.764
1	13.1	16.4	
2	31.1	31.1	
3	52.5	45.9	

Values are % or mean ± SD.
TASC = TransAtlantic Inter-Society Consensus.

TABLE 3 Outcomes of the SF-36 Questionnaire at Baseline and 1-Month and 12-Month Follow-Up, for Both Study Groups

	Pre-Operative	1 Month	12 Months	p Value Pre-Operative vs. 1 Month	p Value Pre-Operative vs. 12 Months
Physical functioning					
Surgical	42.8	54.3	59.4	0.114	0.055
Endoluminal	43.7	65.8	67.8	<0.001	<0.001
Social functioning					
Surgical	67.8	67.2	75.6	0.289	0.952
Endoluminal	66.7	76.5	80.3	0.042	0.060
Role functioning/physical					
Surgical	39.2	37.2	67.7	0.440	0.003
Endoluminal	30.3	52.9	67.9	0.003	<0.001
Role functioning/emotional					
Surgical	72.4	63.0	84.9	0.183	0.088
Endoluminal	57.7	73.3	78.3	0.045	0.392
Mental health					
Surgical	79.1*	76.6	82.5	0.297	0.849
Endoluminal	68.2	79.4	77.4	0.001	0.205
Energy/fatigue					
Surgical	62.0	64.8	67.3	0.476	0.861
Endoluminal	57.2	66.9	66.3	<0.001	0.016
Pain					
Surgical	47.6	62.7	72.3	0.017	<0.001
Endoluminal	41.5	70.5	74.6	<0.001	<0.001
General health perception					
Surgical	54.8	61.3	57.5	0.032	0.865
Endoluminal	57.0	65.7	63.2	0.002	0.045
Health change					
Surgical	37.5*	64.1	58.5	<0.001	<0.001
Endoluminal	45.6	64.7	69.7*	<0.001	<0.001

Values are %. *p < 0.05 between study groups at the different time points.
SF-36 = 36-Item Short Form Survey.

TABLE 4 Outcomes of the WIQ in Patients With Intermittent Claudication at Baseline and 1-Month and 12-Month Follow-Up, for Both Study Groups

	Pre-Operative	1 Month	12 Months	p Value Pre-Operative vs. 1 Month	p Value Pre-Operative vs. 12 Months
Distance					
Surgical	20.7	52.5	65.0	<0.001	<0.001
Endoluminal	22.2	67.3	70.2	<0.001	<0.001
Speed					
Surgical	29.8	39.3	57.3	0.107	<0.001
Endoluminal	32.0	60.0*	59.9	<0.001	<0.001
Stairs					
Surgical	48.1	57.4	64.6*	0.252	0.012
Endoluminal	55.9	77.2*	79.3	<0.001	<0.001
Total WIQ score					
Surgical	33.0	47.6	62.3	0.017	<0.001
Endoluminal	36.7	68.5*	67.2	<0.001	<0.001

Values are %. *p < 0.05 between study groups at the different time points.
WIQ = Walking Impairment Questionnaire.

PROCEDURAL DATA. Technical success was achieved in 93.4% of patients in the endoluminal group versus 100% in the surgical group (p = 0.039). In the 6 technical failures in the endoluminal group, distal reentry was not achieved. Eventually, 4 patients (6.5%) were crossed over from endoluminal to surgical bypass. In the surgical group 67.7% of patients (n = 42) had a suitable vein and the remaining patients (n = 20) were treated with a prosthetic graft (all polytetrafluoroethylene, except 1 polyester). The endograft diameters of patients in whom 1 size of stent grafts was used were 5 mm (n = 4, 7.0%), 6 mm (n = 32, 56.1%), 7 mm (n = 7, 12.3%), and 8 mm (n = 1, 1.8%). In 13 patients stents with different diameters were used to cover the lesion, namely 8 mm and 7 mm (n = 1, 1.8%), 7 mm and 6 mm (n = 7, 12.3%), and 6 mm and 5 mm (n = 5, 8.8%). In 14 patients only 1 endograft was used (24.6%), 2 endografts were placed in 41 patients (71.9%), and 2 patients needed 3 endografts to cover the entire lesion (3.5%). Additional endarterectomy of the common femoral artery or the femoral bifurcation was performed in 37.1% of the endoluminal-treated patients and 21.0% of the surgical-treated patients (p = 0.048). Other additional procedures included wound debridement, minor amputation (n = 2 in the endoluminal group and n = 1 in the surgical group), popliteal angioplasty or endarterectomy (n = 3 in the endoluminal group and n = 2 in the surgical group), or infrapopliteal angioplasty (n = 3 in the endoluminal group only).

Post-procedural ABI significantly increased in both groups from 0.57 ± 0.12 to 0.92 ± 0.16 in the endoluminal and from 0.57 ± 0.13 to 0.91 ± 0.18 in the surgical group (both p < 0.001). Hospital stay was significantly shorter in the endoluminal group (6.0 ± 4.4 days vs. 3.7 ± 3.4 days; p = 0.002), and less patients in the endoluminal group needed transfer to the medium or intensive care unit (not all hospitals had separated departments).

MORBIDITY AND MORTALITY. The total number of complications (Table 5) was significantly higher in the surgical bypass group compared with the endoluminal group, as was the 30-day morbidity rate. The vast majority of complications were minor and resolved without treatment. In both groups 5 complications resulted in a procedure-related serious adverse event. In the endoluminal group 2 dislocated closure devices resulted in reintervention and 2 patients were re-admitted for wound infections (treated with intravenous antibiotics) and another patient's hospitalization was prolonged because of pancreatitis. In the surgical group these included 1 patient in whom a reintervention for occlusion was performed, 1 patient with reintervention for occlusion and a deep

TABLE 5 Overview of Morbidity Until 30-Day Follow-Up for Both Study Groups

	Surgical Bypass	Endoluminal Bypass	p Value
Total complications	61	25	0.048
Patients with ≥1 complication	34 (54.8)	19 (31.1)	0.008
Patients with complication that resulted in SAE	5	5	0.368
Complications per patient	1 (0–5)	1 (0–3)	0.002
Wound infection	15	4	0.007
Seroma	4	1	0.177
Wound blister	1	0	0.319
Hematoma	7	3	0.196
Rebleeding	3	0	0.082
Luxation of closure device	0	2	0.151
Numbness	10	2	0.016
Edema	16	5	0.009
Neuralgia	1	3	0.301
Other complication	4	5	0.710
Renal function deterioration and hyperkalemia	1	1	
Congestive heart failure	1	1	
Arrhythmia	1	1	
Delirium	0	1	
Deep venous thrombosis	1	0	
Reperfusion pain	0	1	
Fever (causa ignota)	1	0	

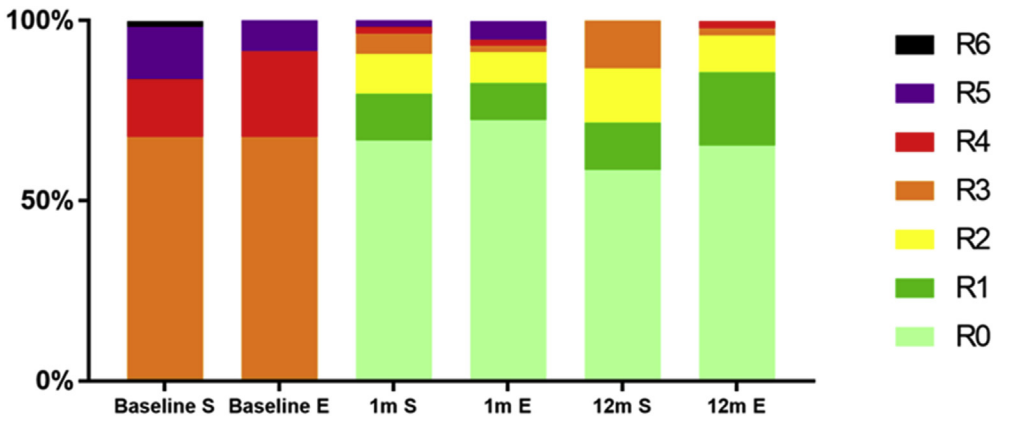
Values are n, n (%), or median (range).
SAE = serious adverse event.

venous thrombosis, 1 patient with neuropathic pain for which the patient was hospitalized (and treated with intravenous esketamine hydrochloride), a patient readmitted for wound infection and treated with debridement and intravenous antibiotics, and another patient readmitted for rebleed treated with compression, but further complicated by renal function disorder and hyperkalemia. In addition, there were no differences in the overall serious adverse event rate, when including all medical conditions that required readmission, regardless of whether they were procedure related. There was no 30-day mortality in either group. At 12 months, 1 patient was deceased in the endoluminal group due to respiratory failure and 2 patients in the surgical group, both related to cancer ($p = 0.569$).

CLINICAL OUTCOME. ABI significantly improved in both groups after intervention (endoluminal group: $+0.37 \pm 0.03$ and surgical group: $+0.35 \pm 0.03$) without differences between groups at any time point.

At 30-day follow-up, there was an improvement in the Rutherford category in 55 patients (93.2%) in the endoluminal group and 50 patients (92.6%) in the surgical group ($p = 0.992$). There were no significant differences in Rutherford category between groups at any time point (Figure 2). At 1 year both groups showed a significant improvement in Rutherford category compared with baseline (98.1% and 98.0% of patients in the endoluminal and surgical groups, respectively; $p = 0.955$). At 1 year, over 50% of patients in both groups were asymptomatic for the treated leg (65.3% and 58.5% for endoluminal and surgical groups, respectively). Moreover, none of the patients showed a deteriorated Rutherford category compared with baseline. Between 1 and 12 months an improvement was observed in 19.6% (n = 19) in the

FIGURE 2 Evolution of the Rutherford Category



Bar chart presenting the Rutherford stages at baseline as well as 1-month and 12-month follow-up. E = endoluminal bypass; S = surgical bypass.

endoluminal group and 10.4% (n = 5) in the surgical group, and approximately 50% of patients in both groups did not change in Rutherford category. In the endoluminal group 28.3% (n = 13) of patients showed a deterioration in clinical category versus 35.4% (n = 17) in the surgical group (p = 0.424) between 1 and 12 months.

At baseline, ulcerations were present at the time of screening in 11 in the endoluminal and 10 patients in the surgical group, mostly located at the level of the toes. Ulcerations tended to be larger in the endoluminal group (median in both groups was 10 mm, but the range in the surgical group was 2 to 10, compared with 2 to 40 in the endoluminal group; p = 0.220). Four patients had no information available regarding healing of the ulcer (3 went to another hospital or withdrew informed consent during follow-up, 1 patient experienced and eventually died from progressive respiratory failure 4 months after treatment). All other ulcerations healed with a median time to complete healing of 3.0 months (range: 1.3 to 6.7 months) in the endoluminal group and 1.8 months (range: 0 to 6.4 months; 1 ulcer was already healed at time of treatment) in the surgical group (p = 0.144). Minor amputations were performed during the first 3 months only in patients that presented with Rutherford stage 5 or 6 at baseline (n = 2 in the endoluminal group and n = 1 in the surgical group). No major amputations were performed through 1-year follow-up.

QUALITY OF LIFE. At 1 week the QoL (SF-36) was significantly better in the endoluminal group compared with the surgical group (50.2 vs. 37.1; p = 0.011) Overall, WIQ scores, assessed in patients with IC, were significantly better in the endoluminal compared with the surgical group (Table 4). The endoluminal group showed an earlier improvement compared with the surgical group. At 1 year, an improvement in most domains of the SF-36 was observed in both groups compared with baseline and no significant differences in reported QoL between groups, except for experienced health change, in favor of the endoluminal group. At 1 year there was a significant improvement in all domains of the WIQ scores in patients with IC in both groups compared with baseline, while the stairs domain remained significantly better in the endoluminal group compared with the surgical group.

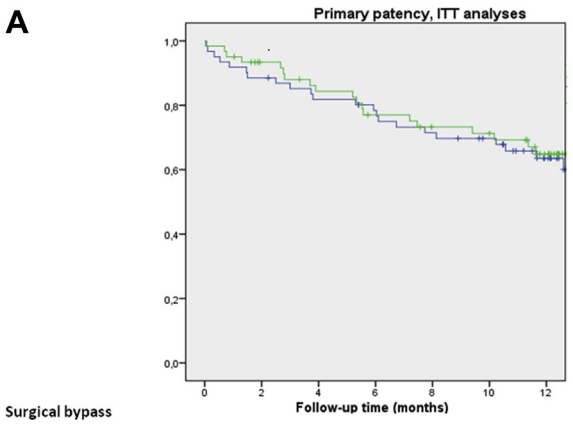
PATENCY RATES AND REINTERVENTIONS. At all measured time points through 1 year, there were no significant differences in primary, primary-assisted, and secondary patency between groups, based on the intention-to-treat analyses (Figures 3 to 5). At 12 months the primary, primary-assisted, and secondary patency for the endoluminal group were 64.8%, 78.1%, and 85.9% and for the surgical group were 63.6%, 79.8%, and 83.3%, respectively. There were also no differences in the number of reinterventions performed or time to failure. When we compared venous bypasses only to the endoluminal bypass, there were also no significant differences in primary and assisted-primary patency between groups, but secondary patency rate was better in the endoluminal group at 6 months only (88.0% vs. 93.9%; p = 0.030). In 2 of the early failures in the surgical group there were procedural complications; in 1 patient a bleeding of the venous conduit occurred during tunneling and in the other the great saphenous vein was twisted, leading to immediate failure, which were treated successfully. Freedom from clinically driven reintervention at 12 months was 77.0% in the endoluminal group compared with 70.7% in the surgical group (p = 0.455), based on an intention-to-treat analysis (Figure 6). Also, no difference was observed when analyzed per protocol.

At 1 year, a total of 23 reinterventions were performed in 17 patients in the endoluminal group (27.9%) and 28 reinterventions were performed in 18 patients (29.0%) in the surgical group. Median time to reintervention was 5.3 months (range: 0.0 to 12.9 months) in the endoluminal versus 3.7 months (range: 0.1 to 11.7 months) in the surgical group (p = 0.666).

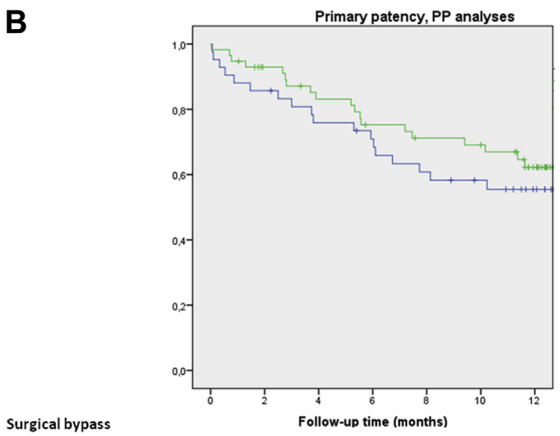
DISCUSSION

In the present study we have shown that heparin-bonded endoluminal bypass is related to a shorter admission time, a faster improvement in QoL, less morbidity, and similar patency rates at 1 year when compared with open surgical bypass in a group of patients that were treated for long complex femoropopliteal arterial lesions. This is the first randomized trial that has shown superiority of endovascular treatment over open surgery with regard to these QoL features, although these results could be anticipated. Historically, venous bypass surgery has been considered the gold standard in terms of long-term patency. For many patients, however, this may not be worth the increased morbidity of an open surgical procedure compared with endovascular methods. Besides, a suitable vein is not always present. The current study is relevant to understanding these tradeoffs and an evaluation of daily practice, including prosthetic bypasses.

FIGURE 3 Primary Patency for the ITT and PP Analyses



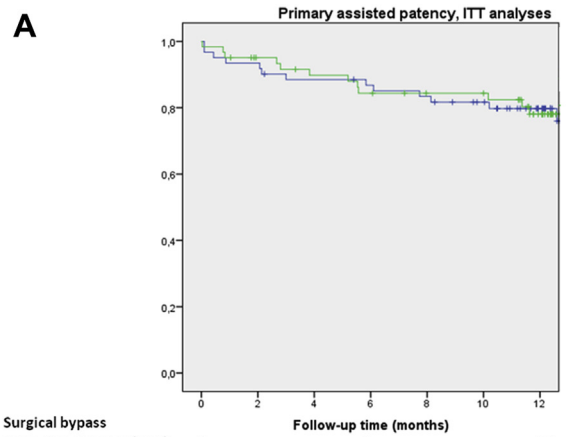
Surgical bypass			
Primary patency (PP)	0	6	12
No. At Risk	62	36	28
Patency (%)	100	79.6	63.6
SE	0.0	0.053	0.064
Endoluminal bypass			
Primary patency (PP)	0	6	12
No. At Risk	63	37	29
Patency (%)	100	77.9	64.8
SE	0.0	0.057	0.066



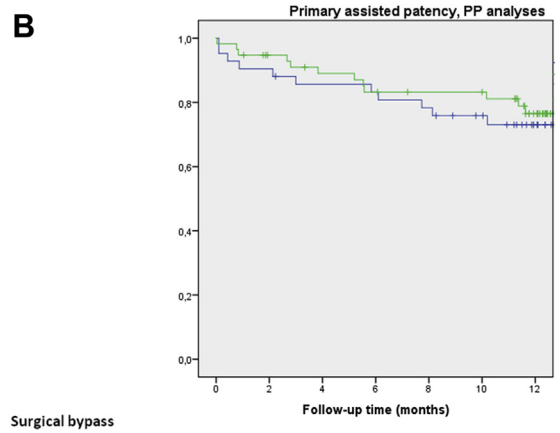
Surgical bypass			
Prim. Patency (PP)	0	6	12
No. At Risk	42	39	42
Patency (%)	100	72.5	55.5
SE	0.0	0.073	0.079
Endoluminal bypass			
Prim. Patency (PP)	0	6	12
No. At Risk	57	40	35
Patency (%)	100	74.0	58.9
SE	0.0	0.060	0.070

(A) Kaplan-Meier curve presenting the primary patency for the surgical **(blue)** and endoluminal **(green)** groups during the 12-month follow-up according to ITT analyses. **(B)** Kaplan-Meier curve presenting the primary patency for the surgical **(blue)** and endoluminal **(green)** groups during the 12-month follow-up according to PP analysis. Abbreviations as in Figure 1.

FIGURE 4 Primary-Assisted Patency for the ITT and PP Analyses



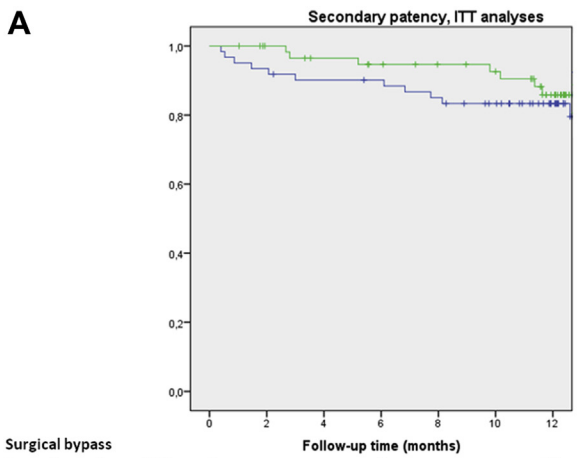
Surgical bypass			
Prim. Ass. Patency (PAP)	0	6	12
No. At Risk	62	39	42
Patency (%)	100	86.3	79.8
SE	0.0	0.045	0.052
Endoluminal bypass			
Prim. Ass. Patency (PAP)	0	6	12
No. At Risk	63	40	35
Patency (%)	100	85.0	78.1
SE	0.0	0.050	0.057



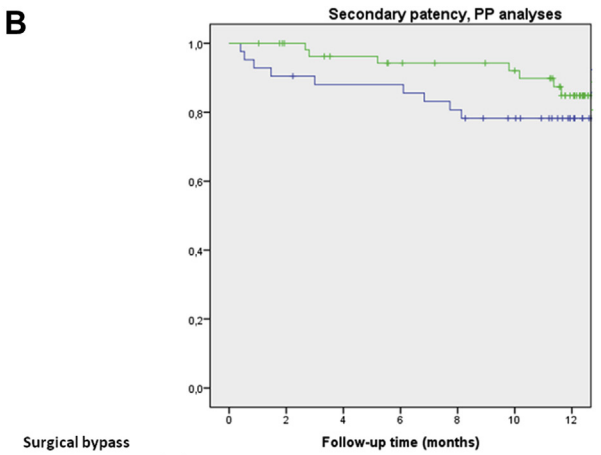
Surgical bypass			
Prim. Ass. Patency (PAP)	0	6	12
No. At Risk	42	39	42
Patency (%)	100	84.6	75.9
SE	0.0	0.058	0.070
Endoluminal bypass			
Prim. Ass. Patency (PAP)	0	6	12
No. At Risk	57	40	35
Patency (%)	100	83.7	76.5
SE	0.0	0.051	0.060

(A) Kaplan-Meier curve presenting the primary-assisted patency for the surgical **(blue)** and endoluminal **(green)** groups during the 12-month follow-up according to ITT analyses. **(B)** Kaplan-Meier curve presenting the primary-assisted patency for the surgical **(blue)** and endoluminal **(green)** groups during the 12-month follow-up according to PP analysis. Abbreviations as in Figure 1.

FIGURE 5 Secondary Patency for the ITT and PP Analyses



Surgical bypass			
Secondary patency (SP)	0	6	12
No. At Risk	62	54	49
Patency (%)	100	90.1	83.3
SE	0.0	0.038	0.048
Endoluminal bypass			
Secondary patency (SP)	0	6	12
No. At Risk	63	45	36
Patency (%)	100	94.3	85.9
SE	0.0	0.032	0.050



Surgical bypass			
Secondary patency (SP)	0	6	12
No. At Risk	42	28	20
Patency (%)	100	88.0	78.2
SE	0.0	0.050	0.064
Endoluminal bypass			
Secondary patency (SP)	0	6	12
No. At Risk	57	38	26
Patency (%)	100	93.9	84.8
SE	0.0	0.032	0.053

(A) Kaplan-Meier curve presenting the secondary patency for the surgical **(blue)** and endoluminal **(green)** groups during the 12-month follow-up according to ITT analyses. **(B)** Kaplan Meier curve presenting the secondary patency for the surgical **(blue)** and endoluminal **(green)** groups during the 12-month follow-up according to PP analysis. Abbreviations as in Figure 1.

Clinical outcome measures are increasingly considered to be at least as important as the classic patency parameter and as such the current study is relevant for the decision-making process in the frail vascular patients. Although walking distance and QoL are most appropriate outcome measures for IC, wound healing and limb salvage are the key issues for patients with CLI. In patients with CLI wound healing occurred in all, and the limb salvage rate was 100% in both groups. This also implies that the potential overstenting of collateral arteries in the endoluminal bypass group did not lead to amputations in patients with an occlusion. This is in accord with a previous study on the outcome of failed endografts (13). At 30 days, patients in the endoluminal bypass group had a significantly better general and disease-specific QoL, as reflected by the SF-36 and WIQ scores, whereas these differences largely disappeared between 1-month and 1-year follow-up. This suggests that the midterm clinical treatment effect of both techniques is similar, but that the morbidity of open surgery delays the improvement. This would advocate an endovascular first strategy also in patients with extensive disease, particularly because endovascular treatment does not reduce surgical options afterward.

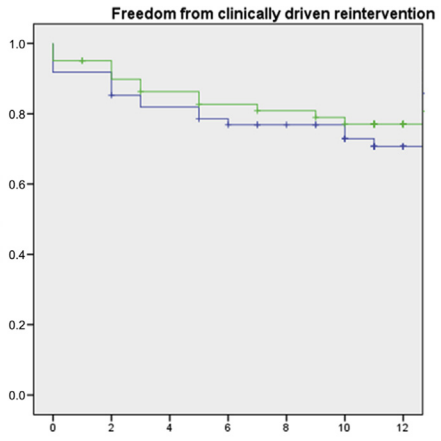
The frailty of the study cohort is reflected by the high morbidity rate, particularly in the surgical arm, although most complications were minor and did not require treatment, such as hematoma not requiring reintervention and edema. Nevertheless, such complications may cause prolonged discomfort for the patient, although a relation with QoL has not been found (14). The morbidity rate seems to be higher in the current study as compared with previous literature, reporting a morbidity rate of 37% after bypass surgery (15); the authors, however, clearly demonstrated that morbidity was inconsistently reported and definitions were often lacking, which likely caused an underestimation of the true incidence of complications after bypass surgery. We are aware that we report complications more extensively than most reports.

We did not observe differences in patency rates between groups up to 1-year follow-up. As the study was terminated before reaching the sample size for the primary patency endpoint, due to a low inclusion rate, noninferiority cannot be claimed on this endpoint. Nevertheless, with the available data there are no indications that 1 of the arms would become superior over the other with a larger sample size. The primary patency rate was lower than anticipated,

particularly in the surgical arm. The data for the endoluminal group are in line with another study focusing on performance and safety of the 25-cm Viabahn endoprosthesis for long lesions, with a 1-year primary patency of 67% (9), but they were lower when compared with the recently published Japanese trial (6), although comparison with our study is hampered by the fact that the Japanese registry consisted of IC patients only with Rutherford stages 2 and 3 and with lesions mainly classified as TASC II type B and C, where the majority of patients had TASC II type D lesions and over 30% of patients with CLI. One of their exclusion criteria was unsuccessful pre-dilation of the lesion, which was not the case in our study. The primary patency in both our study groups could have been influenced by our strictly followed protocol including repeated ultrasound investigations, according to the current standard, and in case of a stenosis with a peak systolic velocity ratio ≥2.5 a reintervention was scheduled, per protocol. This would shift the primary patency to primary-assisted patency, which represents freedom from occlusion, and these data are more in line with the expected rates. Many studies on femoropopliteal bypass surgery were performed more than 2 decades ago, in an era where the assessment of patency was not standardized and often relied on clinical investigation only. If no imaging is performed, asymptomatic stenosis could be missed and consequently not treated, preserving primary patency.

Technical failure in the endoluminal group was always due to the inability to pass the lesion. Once wire access was gained, all devices were successfully deployed to treat the intended location. Unfortunately, data on the use of dedicated passing and re-entry devices were not captured in the present study. With the ongoing improvement of these devices the technical success rate is likely to increase in the future. It should be noted, that, although it did not impact technical success, vein with an appropriate diameter was available in only 2 of 3 of the patients randomized to bypass. This has also been observed in other bypass trials; in the REVAS (Remote endarterectomy versus supragenicular bypass surgery for long occlusions of the superficial femoral artery) trial only 45% of patients had a suitable vein (16). Mandatory preoperative assessment of the vein with duplex could have increased the number of patients with a suitable vein, but a potential underestimation of the diameter could also have incorrectly excluded patients. The vast majority of patients were treated with an endograft ≥6 mm, and we could not find a relation between the used stent diameter and outcome, which is in accord with previous studies (4,17). Interestingly, a concomitant endarterectomy of the common femoral artery was a predictor for success in both study arms resulting in better patency rates compared with those without a concomitant endarterectomy (data not shown). Although no stenotic lesions were present at the location of the proximal anastomosis or the access site, the state of atherosclerotic disease in this segment seems to be a key factor impacting outcomes. Removing calcium could positively affect local flow patterns in the inflow section. This unexpected observation warrants further studies focusing on flow and wall shear stress in this area. New treatment modalities have been developed, such as drug eluting stents. One of the ongoing studies is the ZILVERPASS (The Cook Zilver PTX Drug-eluting Stent Versus Bypass Surgery for the Treatment of Femoropopliteal TASC C&D Lesions) study, which has been designed to compare the endovascular strategy, using drug-eluting stents, and

FIGURE 6 Freedom From Clinically Driven Reintervention



Surgical bypass			
	0	6	12
No. At Risk	61	45	32
Freedom CD-TVR (%)	100	76.9	70.7
SE	0.0	0.054	0.060
Endoluminal bypass			
	0	6	12
No. At Risk	61	46	40
Freedom CD-TVR (%)	100	82.7	77.0
SE	0.0	0.0570	0.056

Kaplan-Meier curve presenting the 12-month freedom from clinically driven reintervention during the 12-month follow-up according to intention-to-treat analyses. CD-TVR = clinically driven target vessel revascularization.

prosthetic bypass surgery in long and more complex superficial femoral artery lesions (NCT01952457).

STUDY LIMITATIONS. First, the study was terminated after achieving the sample size necessary for the designed power for the expected QoL, but before reaching that necessary to determine designed non-inferiority in patency outcomes. The enrollment rate during the study period was lower than anticipated and, given the required sample size for the patency endpoint, the projected enrollment period would become unacceptably long. Selection bias might have occurred. Additionally, the proportion lost to follow-up was relatively high, reflecting the frailty of this study population. Although the study was performed in 6 sites, the vast majority of patients were included in only few of them. This suggests that patients, meeting the inclusion criteria, were likely to be missed. Although the power for the primary endpoint health status was achieved, the absolute numbers in each group were limited, rendering the subgroup analyses less reliable. Screen failures were not documented throughout the inclusion period.

CONCLUSIONS

We have shown that heparin-bonded endoluminal bypass when compared with the femoropopliteal bypass, is related to less morbidity, a faster recovery, and improvement in QoL, whereas no differences in patency were observed. Although these results are promising, mid- and long-term results have to be awaited before robust conclusions can be drawn regarding which technique should be standard of care.

ADDRESS FOR CORRESPONDENCE: Dr. Michel M.P.J. Reijnen, Rijnstate Hospital, Department of Surgery, Wagnerlaan 55, P.O. Box 9555, 6800 TA, Arnhem, the Netherlands. E-mail: mmpj.reijnen@gmail.com.

PERSPECTIVES

WHAT IS KNOWN? Endovascular treatment of extensive arterial femoropopliteal disease is increasingly being used. Endovascular treatment options are rapidly expanding and clear treatment algorithms are lacking. Guidelines still advocate bypass surgery for long occlusive femoropopliteal lesions.

WHAT IS NEW? The use of heparin-bonded covered stents is related to fewer complications and faster recovery compared with bypass surgery. Both techniques have similar outcome at 1-year follow-up in terms of QoL and patency.

WHAT IS NEXT? Long-term outcomes of this randomized controlled trial have to be awaited. Head-to-head comparisons with other novel endovascular techniques, including paclitaxel-based technology, are needed.

REFERENCES

1. Zeller T. Current state of endovascular treatment of femoro-popliteal artery disease. Vasc Med 2007;12:223–34.

2. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 Suppl S:S5–67.

3. Committee TS, Jaff MR, White CJ, et al. An Update on Methods for Revascularization and Expansion of the TASC Lesion Classification to Include Below-the-Knee Arteries: A Supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Endovasc Ther 2015;22:663–77.

4. Saxon RR, Chervu A, Jones PA, et al. Heparin-bonded, expanded polytetrafluoroethylene-lined stent graft in the treatment of femoropopliteal artery disease: 1-year results of the VIPER (Viabahn Endoprosthesis with Heparin Bioactive Surface in the Treatment of Superficial Femoral Artery Obstructive Disease) trial. J Vasc Interv Radiol 2013;24:165–73, quiz 174.

5. Lensvelt MM, Fritschy WM, van Oostayen JA, Holewijn S, Zeebregts CJ, Reijnen MM. Results of heparin-bonded ePTFE-covered stents for chronic occlusive superficial femoral artery disease. J Vasc Surg 2012;56:118–25.

6. Ohki T, Kichikawa K, Yokoi H, et al. Outcomes of the Japanese multicenter Viabahn trial of endovascular stent grafting for superficial femoral artery lesions. J Vasc Surg 2017;66:130–42.e1.

7. McQuade K, Gable D, Pearl G, Theune B, Black S. Four-year randomized prospective comparison of percutaneous ePTFE/nitinol self-expanding stent graft versus prosthetic femoral-popliteal bypass in the treatment of superficial femoral artery occlusive disease. J Vasc Surg 2010;52:584–90, discussion 590–1, 591.e1–7.

8. Lammer J, Zeller T, Hausegger KA, et al. Sustained benefit at 2 years for covered stents versus bare-metal stents in long SFA lesions: the VIASTAR trial. Cardiovasc Interv Radiol 2015;38:25–32.

9. Zeller T, Peeters P, Bosiers M, et al. Heparin-bonded stent-graft for the treatment of TASC II C and D femoropopliteal lesions: the Viabahn-25 cm trial. J Endovasc Ther 2014;21:765–74.

10. Lensvelt MM, Holewijn S, Fritschy WM, et al. SUrgical versus PERcutaneous Bypass: SUPERB-trial; Heparin-bonded endoluminal versus surgical femoro-popliteal bypass: study protocol for a randomized controlled trial. Trials 2011;12:178.

11. Burgers JS, Simoons ML, Hoes AW, Stehouwer CD, Stalman WA. [Guideline 'cardiovascular risk management']. Nederlands tijdschrift voor geneeskunde 2007;151:1068–74.

12. Stoner MC, Calligaro KD, Chaer RA, et al. Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease: Executive summary. J Vasc Surg 2016;64:227–8.

13. Lensvelt MM, Golchehr B, Kruse R, et al. Outcome of failed endografts inserted for superficial femoral artery occlusive disease. J Vasc Surg 2013;57:415–20.

14. Ozturk C, te Slaa A, Dolmans DE, et al. Quality of life in perspective to treatment of postoperative edema after peripheral bypass surgery. Ann Vasc Surg 2012;26:373–82.

15. van de Weijer MA, Kruse RR, Schamp K, Zeebregts CJ, Reijnen MM. Morbidity of femoropopliteal bypass surgery. Semin Vasc Surg 2015;28:112–21.

16. Gisbertz SS, Tutein Nolthenius RP, de Borst GJ, et al. Remote endarterectomy versus supragenicular bypass surgery for long occlusions of the superficial femoral artery: medium-term results of a randomized controlled trial (the REVAS trial). Ann Vasc Surg 2010;24:1015–23.

17. Acin F, de Haro J, Bleda S, Varela C, Esparza L. Primary nitinol stenting in femoropopliteal occlusive disease: a meta-analysis of randomized controlled trials. J Endovasc Ther 2012;19:585–95.

KEY WORDS bypass, covered stent, femoropopliteal, patency, quality of life, randomized